



# **Pediatric Focused Safety Review: Keppra<sup>®</sup> (levetiracetam) Pediatric Advisory Committee Meeting April 21, 2014**

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# Outline

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- Pediatric Studies
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- Drug Use Trends
- Safety
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# Background Drug Information

## Keppra® (levetiracetam)

- **Drug:** Keppra® (levetiracetam)
- **Formulations:**
  - 250, 500, 750 and 1000 mg tablets
  - 500 mg and 750 extended-release tablets (adults only)
  - 100 mg/mL solution
  - 500 mg/5 mL single-use vial (adults only)
- **Sponsor:** UCB, Inc.
- **Original Market Approval:** November 30, 1999
- **Pediatric Labeling Change:** December 16, 2011
- **Therapeutic Category:** anti-epileptic

# Background Drug Information, continued

## Keppra® (levetiracetam)

- **Indication:** Adjunctive therapy in the treatment of:
  - Partial onset seizures in patients 1 month of age and older with epilepsy
  - Myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy
  - Primary generalized tonic-clonic seizures in patients 6 years of age and older with idiopathic generalized epilepsy

# Background Drug Information, continued

## Keppra® (levetiracetam)

- **Postmarketing Requirements:**
  - Deferred pediatric study under PREA for a pharmacokinetic and safety study in 30 pediatric patients ages 4 to 16 years for the IV formulation (IV formulation not approved in the pediatric population)
  - Deferred pediatric study under PREA for an open-label, single dose, pharmacokinetic study with Keppra XR in patients ages 12 to 16 years with epilepsy

# Pediatric Studies

## Keppra® (levetiracetam)

### Pediatric Written Request:

- Issued on August 21, 2001, and amended multiple times with last amendment on January 31, 2006
- Included studies to assess the pharmacokinetics, safety and effectiveness of levetiracetam in partial complex seizures in pediatric patients ages 1 month to 16 years of age
- Data in pediatric patients ages 4 to 16 years of age was submitted on December 21, 2004; age group extended on June 21, 2005
- Data in pediatric patients ages 1 month to 4 years of age was submitted on March 18, 2008; age group extended on December 16, 2011
- Pediatric Exclusivity was granted on September June 3, 2008

## **Pediatric Studies, continued**

### **Keppra® (levetiracetam)**

- A double-blind, randomized, multicenter, placebo-controlled, in-patient study examining efficacy as adjunctive treatment of partial seizures in 116 patients 1 month to less than 4 years of age
- A double-blind, a randomized multicenter, placebo-controlled 19-week safety study examining cognitive and neuropsychological effects of levetiracetam as adjunctive treatment in 98 pediatric patients 4 to 16 years of age with partial seizures
- Two multi-center, open-label, long-term, safety studies in 285 pediatric patients between 1 month and 16 years of age

# Pediatric Labeling Change Keppra® (levetiracetam)

## 1 INDICATIONS AND USAGE

Keppra® is indicated for adjunctive therapy in the treatment of partial onset seizures in patients one month of age and older with epilepsy

## 2 DOSAGE AND ADMINISTRATION

### 2.2 Partial Onset Seizures

#### Pediatric Patients

*1 month to < 6 months*

Initiate at 7 mg/kg twice a day and titrate to 21 mg/kg twice a day

*6 months to 4 years*

Initiate at 10 mg/kg twice a day and titrate to 25 mg/kg twice a day



# Pediatric Labeling Change, continued

## Keppra® (levetiracetam)

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Psychiatric Reactions

Updated to include behavioral adverse events noted in clinical trials

- Increased aggressive behavior in pediatric patients ages 4 to 16 years of age
- Increased irritability in pediatric patients 1 month to 4 years of age

#### 5.4 Serious Dermatological Reactions

Updated to include Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)

#### 5.8 Blood Pressure Increases

Diastolic blood pressure increases were seen in the clinical trial of levetiracetam treated patients ages 1 month to 4 years of age

# Pediatric Labeling Change, continued

## Keppra® (levetiracetam)

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

##### Pediatric Patients 4 Years To <16 Years

Updated to include long-term safety data

Most frequently reported adverse events were fatigue, aggression, nasal congestion, decreased appetite, and irritability

##### Pediatric Patients 1 Month To < 4 Years

Somnolence and Irritability were the most commonly reported adverse events

Adverse reactions were usually mild to moderate in intensity

# **Pediatric Labeling Change, continued**

## **Keppra® (levetiracetam)**

### **8 USE IN SPECIFIC POPULATIONS**

#### **8.4 Pediatric Use**

The safety and effectiveness of KEPPRA in the adjunctive treatment of partial onset seizures in pediatric patients age 1 month to 16 years old with epilepsy have been established

# Pediatric Labeling Change, continued

## Keppra® (levetiracetam)

### 12 CLINICAL PHARMACOLOGY

#### 12.3 Pharmacokinetics

##### Specific Populations:

##### *Pediatric Patients*

PK data provided for pediatric patients 1 month to 4 years of age

### 14 CLINICAL STUDIES

#### 14.1 Partial Onset Seizures

##### Effectiveness in Partial Onset Seizures in Pediatric Patients 1 Month to <4 Years with Epilepsy

Includes clinical study data that supported pediatric approval for pediatric patients 1 month to 4 years of age

# **Relevant Safety Labeling, continued**

## **Keppra® (levetiracetam)**

### **5 WARNINGS AND PRECAUTIONS**

- 5.1 Psychiatric Reactions
- 5.2 Suicidal Behavior and Ideation
- 5.3 Somnolence and Fatigue
- 5.4 Serious Dermatological Reactions
- 5.5 Coordination Difficulties
- 5.6 Withdrawal Seizures
- 5.7 Hematologic Abnormalities
- 5.8 Blood Pressure Increases

# Pediatric Drug Utilization

## Keppra® (levetiracetam)

**Nationally Estimated Number of Patients that received a Dispensed Levetiracetam Prescription From U.S. Outpatient Retail Pharmacies, Stratified by Age, June 2010 through May 2013, Aggregate**

	<b>Patients (N)</b>	<b>Share (%)</b>
<b>TOTAL</b>	<b>1,888,877</b>	<b>100.0%</b>
0-17 years	316,430	16.8%
< 1 year	25,077	7.9%
1-5 years	113,011	35.7%
6-12 years	131,369	41.5%
13-17 years	91,730	29.0%
18+ years	1,589,864	84.2%
Unknown Age	699	0.0%

*Subtotals may not sum exactly due to rounding. Because of patients aging during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across years is not advisable and will result in overestimates of patient counts.*

*Source: IMS Vector One®: Total Patient Tracker (TPT). June 2010-May 2013. Extracted October 11, 2013..*

# Pediatric Drug Utilization

## Keppra® (levetiracetam)

**Nationally Estimated Number of Patients with a Hospital Billing for Levetiracetam From U.S. Non-Federal Hospitals, Stratified by Age, June 2010 through May 2013, Aggregate**

	Patients (N)	Share (%)
<b>TOTAL</b>	<b>2,029,204</b>	<b>100.0%</b>
0-17 years	130,013	6.4%
< 1 year	12,912	9.9%
1-5 years	42,543	32.7%
6-12 years	37,309	28.7%
13-17 years	41,563	32.0%
18+ years	1,896,568	93.5%
Unknown Age	4830	0.2%

*Subtotals may not sum exactly due to rounding. Because of patients aging during the study period ("the cohort effect"), patients may be counted more than once in the individual age categories. For this reason, summing across years is not advisable and will result in overestimates of patient counts.*

*Source: IMS INpatient HealthCare Utilization System (IHCaUS). June 2010-May 2013. Extracted October 15, 2013.*

# Pediatric Drug Utilization, continued Keppra® (levetiracetam)

## Prescribing Specialty<sup>1</sup> and Diagnosis<sup>2</sup> June 2010 through May 2013, Aggregate

- Top prescribing specialties for levetiracetam were Neurology (50%), Internal Medicine (11%) and Family Practice (8%)
  - **Pediatric Specialists** accounted for 2.6 % of levetiracetam prescriptions
- Diagnoses related to epilepsy or seizures were the most frequently mentioned diagnoses associated with the use of levetiracetam in pediatric patients across all age groups

<sup>1</sup>IMS, National Prescription Audit (NPA). June 2010-May 2013. Extracted October 11, 2013.

<sup>2</sup>Encuity Research, LLC., Treatment Answers™ Audit. June 2010-May 2013. Extracted October 11, 2013.





# **Postmarketing Pediatric Reports in the FDA Adverse Event Reporting System (FAERS)**

# Review Strategy

## 1. 3 years (June 1, 2010 - May 31, 2013)

- All events
- Serious outcomes\*

## 2. 14 years (Nov 30, 1999 - May 31, 2013)

- Events of interest†
- Serious outcomes\*

\*Serious: Death, hospitalization, life-threatening, and congenital anomaly

†Drug reaction with eosinophilia and systemic symptoms (DRESS), agranulocytosis and bone marrow failure, completed suicide, apnea, interstitial lung disease, and tubulointerstitial nephritis

## Crude Counts for Adult and Pediatric FAERS Reports for the 3 Year Period of June 1, 2010 to May 31, 2013 with Levetiracetam

	All reports (US)	Serious (US) <sup>†</sup>	Death (US)
<b>Adults (≥ 18 years)</b>	3,217 (1,260)	1,906 (703)	413 (231)
<b>Pediatrics (0-17 years)</b>	802 (276)	423 (130) <sup>*</sup>	77 (19)

<sup>†</sup>Serious adverse drug experiences per regulatory definition (CFR 314.80).

<sup>\*</sup>Subset of serious pediatric reports with an outcome of death, life-threatening, hospitalization, and congenital anomaly.



## Descriptive Characteristics of the Pediatric Case Series (Crude Counts) with Levetiracetam (n=423)

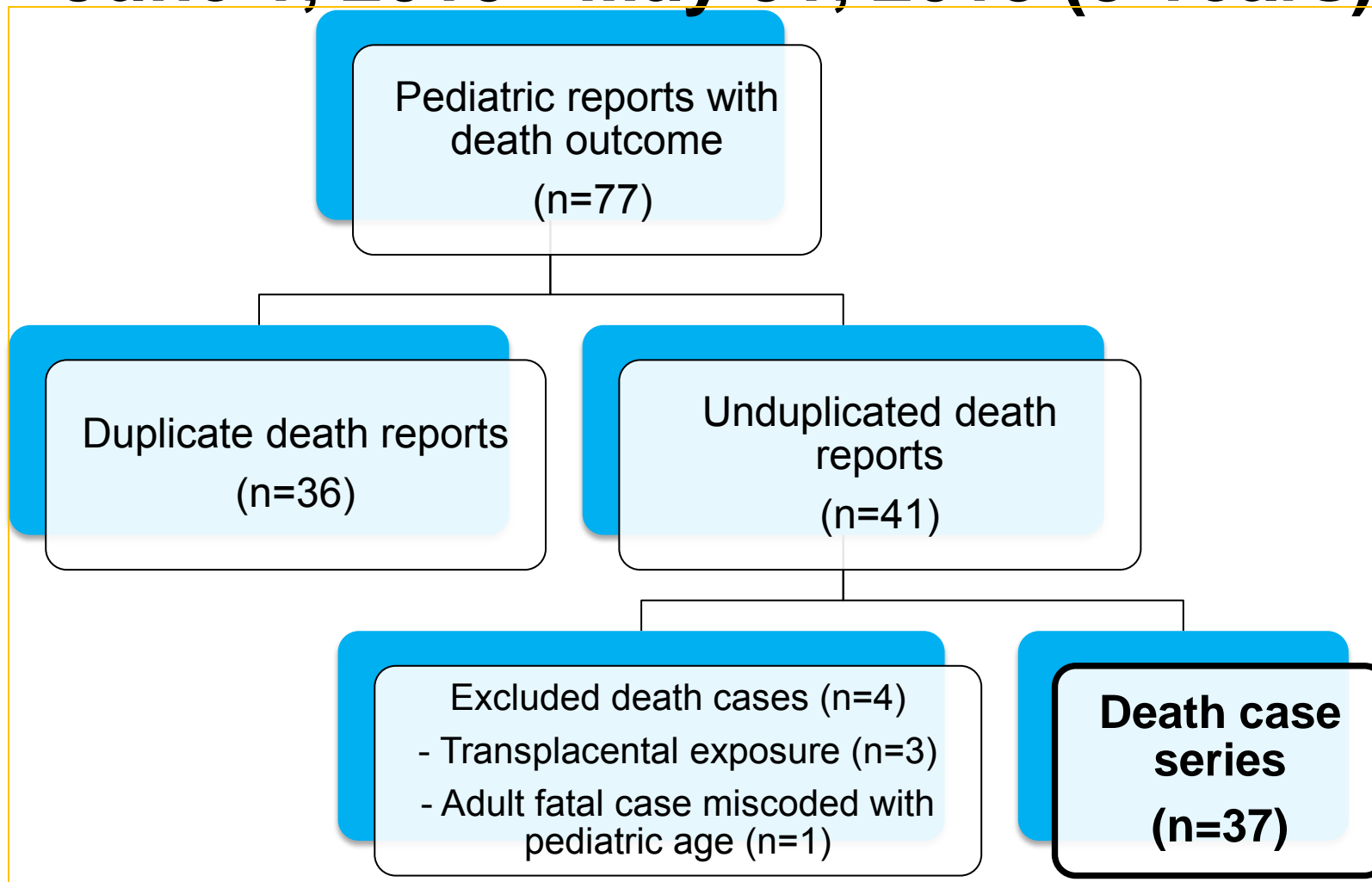
<b>Age</b>	0 - < 1 year	110
	1 - 5 years	93
	6 – 12 years	116
	13 – 17 years	104
<b>Gender</b>	Male	252
	Female	164
	Unknown	7
<b>Country of reporter</b>	United States	150
	Foreign	273
<b>Serious Outcomes*</b>	Death	77
	Life-threatening	33
	Hospitalization	270
	Congenital anomaly	52
<b>Indication(s)</b>	Convulsion	13
	Epilepsy	41
	Miscellaneous seizures	16
	Non-seizure indication	49
	Unknown indication	304

\* A report may include more than one outcome

**Pediatric Cases with Outcome of Death  
June 1, 2010 – May 3, 2013 (3 years)  
Keppra® [levetiracetam]  
(n=77)**

# Pediatric Death Case Selection

## June 1, 2010 - May 31, 2013 (3 Years)



## Pediatric Deaths (n=37)

- ❑ In general, we concluded the causes of death were related to the patient's underlying disease, comorbid conditions, or confounded by other medications, and unlikely related to levetiracetam use
- ❑ While not specified, many cases could be sudden unexplained death in epilepsy (SUDEP)

### SUDEP

- ❑ Sudden death is 20 times more likely to occur in patients with epilepsy than the general population
  - For a diagnosis of SUDEP, one needs to identify a death that is not due to trauma, drowning, status epilepticus, or any other identifiable causes
  - SUDEP usually presents as a patient who is discovered dead, with no identifiable cause
  - The risk of SUDEP increases with the severity of the seizure disorder; in general anticonvulsant treatment may be associated with reduction in the incidence of SUDEP<sup>1</sup>

1. Ryvlin P, Cucherat M, and Rheims S. Risk of sudden unexpected death in epileptic patients with uncontrolled seizures given adjunctive antiepileptic treatment: a meta-analysis of placebo-controlled randomized trials. *Lancet Neurol* 2011;10 (11):961-8.

# Summary of Pediatric Death Cases (n=37)

## Demographics of 37 death cases

- Foreign (28) and domestic (9) cases
- Female (17) and male patients (20)
- Ages ranged from 1 day to 17 years

- ❑ 7 cases were reported in one literature article<sup>2</sup> where the authors collected post-mortem levetiracetam data and the author concluded that none of the deaths were attributed to levetiracetam
- ❑ 30 cases were sorted into categories based on reported cause of death:
  - Cardiorespiratory arrest (13)
  - Unknown and other events (6)
  - Underlying disease (5)
  - Sudden death (3)
  - Completed suicide (2)
  - Hepatic failure (1)

<sup>2</sup>Bishop-Freeman SC et al., Postmortem Levetiracetam (Keppra) Data from North Carolina. Anal Toxicol 2012; 36(6):522-28.



# Summary of Pediatric Deaths (Cont'd)

## Cardiorespiratory arrest (n=13)

- ❑ Ages: 8 months – 15 years
  - Intractable seizure (6)
  - Infection and aspiration pneumonia (6)
  - CNS lesions with loss of consciousness and respiratory arrest that was witnessed by medical staff before the patient died (1)

# Summary of Pediatric Deaths (Cont'd)

## Unknown and other causes of death (n=6)

- ❑ Ages: 1 and 9 day; 8, 16 (2) and 17 years
  - A one day old with infantile free sialic acid storage disease experienced hepatosplenomegaly and intractable seizures (1)
  - A 9 day old experienced status crisis and cerebral necrosis from hypoxic ischemia, the cause of death was reported to be intestinal ischemia (1)
  - An 8 year old experienced “convulsive crisis and status epilepticus” that was refractory to multiple AEDs, infection and hemodynamic impairment and finally developed multiple organ failure (1)
  - A 16 year old diagnosed with fatal viral sclerosing panencephalitis one year after starting levetiracetam and multiple other drugs (1)
  - A 16 year old died of an unknown cause, although status epilepticus was suspected (1)
  - A 17 year old with craniocerebral injury and complex seizure history died; autopsy revealed unknown cause of death (1)

# Summary of Pediatric Deaths (Cont'd)

## Underlying disease (n=5)

- ❑ Ages: 3 and 5 months; 6, 8, and 16 years old
  - Unspecified “severe hereditary disease” (2)
  - Underlying brain lesion (1)
  - Cardiomyopathy and heart failure (1)
  - Congenital “cardiopathy” and multiple organ failure (1)

# Summary of Pediatric Deaths (Cont'd)

## Sudden death (n=3)

- ❑ Ages: 8 months and 7 and 10 years
  - An 8 month old experienced intractable seizure (60/day) not controlled with multiple AEDs. On an unspecified date, she developed neurologic impairment with marked axial hypotonia, absence of visual contact, and lack of head control. Two months later, she died suddenly without evidence of seizure activity. Autopsy revealed pulmonary edema (1)
  - A 7 year old experienced recurrent nonconvulsive status epilepticus (NCSE) which required hospitalization, drug induced coma, and electroconvulsive therapy (ECT); she was released 15 days later. Eleven weeks later, her EEG and mental status continued to improve; however, she died suddenly (1)
  - A 10 year old female was found “lifeless” in bed and pronounced dead on the way to the hospital (1)

# Summary of Pediatric Deaths (Cont'd)

## Completed suicide [unlabeled] (n=2)

- ❑ Ages: 13 and 14 years
  - A 13 year old with a history of ADHD, psychosis, recent difficult social situation, and family history of suicide received 8 days of levetiracetam before completing suicide (1)
  - A 14 year old with an unknown medical history received levetiracetam for 5 months with a “dose increase” at an unknown time showed irritability and behavior disorders before completing suicide (1)

## Hepatic failure [labeled] (n=1)

- ❑ A 3 year old received levetiracetam and multiple other AEDs to treat status epilepticus for 3 days and experienced acute liver failure and encephalopathy that required a liver transplant and he died 6 days later; no further details were provided

# **Pediatric Non-Fatal Serious Reports June 1, 2010 – May 31, 2013 (3 years) Keppra® [levetiracetam] (n=346)**

# Pediatric Non-Fatal Serious Reports (n=346)

## No new safety concerns identified

- ❑ Majority of the events are labeled, closely related to labeled terms, or may be associated with primary disease processes, the syndrome of epilepsy, or confounded by other medications
- ❑ Most frequently reported adverse events: aggression, somnolence, status epilepticus, vomiting, fatigue, thrombocytopenia, abnormal behavior, rash, ataxia, and gait disturbance
  - These events were frequently reported in pediatric patients during clinical trials, and are described in the Warnings and Precautions, or Adverse Reactions section
  - Status epilepticus, the only unlabeled event, is not unexpected given the medical condition being treated

**Pediatric  
Unlabeled Events of Interest  
11/30/1999 - 5/31/2013 (14 years)  
Keppra® (levetiracetam)**



# Unlabeled Events of Interest

## No new safety concerns identified in pediatric patients

- ☐ Drug reaction with eosinophilia and systemic symptoms [DRESS] (5)
- ☐ Agranulocytosis and bone marrow failure (4)
- ☐ Completed suicide (2)\*
- ☐ Apnea (1)
- ☐ Interstitial lung disease (1)
- ☐ Tubulointerstitial nephritis (1)

\*Discussed previously

# Unlabeled Events of Interest (Cont'd)

## DRESS (n=5)

- ❑ Levetiracetam's contribution to DRESS could not be determined
  - Confounded by other medications: carbamazepine, lacosamide, phenytoin, or vancomycin which are known to cause DRESS (4)
  - Resolved after discontinuation of levetiracetam and metronidazole (both unlabeled) with improvement of symptoms (1)
- ❑ Cases of DRESS are under FDA review in response to the sponsor's request for labeling change in all age groups

# Unlabeled Events of Interest (cont'd)

## Agranulocytosis and bone marrow failure (n=4)

- ❑ Levetiracetam's contribution to agranulocytosis and bone marrow failure could not be determined
  - Agranulocytosis cases were confounded by concomitant use of amoxicillin/clavulanate and esomeprazole which are both labeled for agranulocytosis (2)
  - Bone marrow failure cases were confounded by chemotherapy or felbamate, which are labeled for bone marrow disorders (2)
- ❑ Cases of agranulocytosis are under FDA review in response to the sponsor's request for labeling change in all age groups

# Unlabeled Events of Interest (cont'd)

## Apnea (n=1)

- ❑ A 5 year old female with mitochondrial encephalomyopathy experienced apnea and required ventilator support temporal to levetiracetam use; she recovered with Keppra dose reduction and respiratory support

## Interstitial Lung Disease (n=1)

- ❑ A 9 year old experienced interstitial pneumonitis during the use of “low dose” levetiracetam, with resolution of symptoms subsequent to discontinuing levetiracetam and starting steroids

## Tubulointerstitial nephritis (n=1)

- ❑ A 17 year old female reported a baseline serum creatinine of 0.7 and 10 days after levetiracetam creatinine increased to 3.3 with symptoms including abdominal pain, vomiting . . . ; event resolved with discontinuing levetiracetam and starting steroids

# Summary

- ❑ **No new safety concerns identified in pediatric patients**
  - Pediatric death cases
  - Non-fatal serious pediatric reports from the last three years
  - Events of interest cases since levetiracetam approval
- ❑ The sponsor has proposed new addition of safety information to the labeling on agranulocytosis and DRESS in all ages which are under review

# Summary of Safety Reviews

## Keppra® (levetiracetam)

- This concludes the pediatric focused safety review of FAERS reports
- Labeling has been updated to include the studies performed under Best Pharmaceuticals in Children Act (BPCA)
- No new safety signals were identified
- FDA recommends continued routine monitoring
- Does the committee concur?

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